Design of a Pembrolizumab Manufacturing Plant in Ireland Using Continuous Bioprocess Technology and Single-Use Bioreactors
(Technical Paper)

The Relationship Between Patents on Insulin, Drug Access, and Innovation in the United States
(STS Paper)

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction:

A specific class of drugs called protein therapeutics makes up a large percentage of the types of medicines that pharmaceutical companies produce annually. Data indicates that the market value for the protein therapeutics will increase from $140,109 million in 2016 to $217,591 million by 2023 (MarketWatch, 2019). With the market value for widely popular protein therapeutics increasing, it has become more important to find ways in which to process, these drugs and understand their social implications. The technical proposal will focus on the design of chemical plant, for the specific protein therapeutic, Pembrolizumab, also called Keytruda, used to treat cancer (Merck & Co., 2019). Keytruda is a relatively new type of protein therapeutic that utilizes mAbs, allowing the body's immune system to identify and kill cancer cells (Melanoma Research, 2016). It is predicted that Keytruda could exceed the sales of all other prescriptions worldwide in 2023, emphasizing the need for ways to increase its production (Nathan-Kazis, 2019).

The STS proposal will focus on the protein therapeutic, insulin, and the role that patents play in the pricing, availability, and innovative development of the drug in the United States. Research now points to 45 percent of patients having to go without insulin for a certain period of time (Rappold, 2019). Additionally, data suggest that insulin list prices have tripled, and have increased by 64 percent from 2002 to January 2014 (Rosenfeld, 2019). The increasing price of insulin has led to a lack of availability of the drug and, as a result, patient deaths. Analyzing the role that patents play in situation, and how patents have encouraged companies to innovate are extremely important in understanding their impact in relation to insulin.

Technical Topic (Authors: Revathi Mohan, Clayton Buruss, Brian Abt, Summer Xu, Noah Rushin):

The cancer immunotherapy drug Keytruda, also known as pembrolizumab, is a checkpoint inhibitor monoclonal antibody (mAb) manufactured by Merck. Cancer is the second leading cause of death in the U.S., with the number of cancer cases expected to rise from 14.1 million in 2012 to 23.6 million in 2030 (National Cancer Institute, 2015). Associated with this increase in disease rates is a shift in technology within the pharmaceutical industry in hopes of addressing these disease rates. Antibody-based drugs, specifically, have risen as the fastest growing class of protein therapeutics due to their increased efficacy, decreased immunogenicity, improved deliverability, and decreased potential to adversely affect normal biological processes compared to standard chemotherapy treatments(Awwad & Angkawinitwong, 2018).

Keytruda works by blocking the PD-1 pathway. By doing so, immunogenic T-cells can locate cancer cells and induce a natural immune response (Merck & Co., 2019). This novel mechanism of action, coupled with low side effects when compared to chemotherapy, makes Keytruda an extremely promising drug in the fight against many types of cancer. Although Keytruda was initially used to treat lung cancer, it has and is continuing to receive increased market approvals for oncology indications. Due to increasing global demand, Merck announced that it will build a $300 million Keytruda manufacturing facility in Dublin, Ireland. The facility will begin manufacturing operations in 2022 (The Irish Times, 2018).

The current process of mAb production includes culturing mammalian cells that produce the recombinant mAb protein in a large steel batch reactor. This is followed by several unit operations to separate the desired product from the fermentation media (Gillepsie, et al., 2014). These batch steel reactors are large, expensive to operate, and have low product yields. They also

require extensive cleaning protocols involving potent and abrasive chemicals, which are necessary to appropriately sterilize the reactor (W. Runstadler, 1992). A lack of the aforementioned changes to process design can contribute to high production costs, decrease the ability of a single facility to produce different drug products, and cause additional conflicts with environmental regulations due to the potency of the reactor cleaning chemicals.

We plan to design the new Merck Keytruda production facility with perfusion reactors and single-use bags. Incorporating single-use reactor bags will decrease the need for extensive cleaning protocols, save time, reduce employment costs, improve compliance with environmental regulations, improve the modularity of the manufacturing facility, and ensure product purity between batches (Jacquemart, et al., 2016). Using a perfusion reactor will allow continuous production of Keytruda, rather than the production of the drug in batches. Perfusion bioreactors culture cells over longer periods by continuously feeding and removing media while keeping cells in culture (Bielser, Wolf, Souquet, Broly, & Morbidelli, 2018). This continuous production will increase product yields and subsequently decrease production costs. Perfusion reactors also traditionally require fewer operators, further decreasing production costs (W. Runstadler, 1992).

Therefore, we propose the design of a Keytruda manufacturing plant that uses the aforementioned manufacturing strategies. This process will start with the fermentation of Chinese hamster ovary (CHO) cells with incorporated recombinant DNA for Keytruda. These cells will be grown in serum-free CHO media in a stirred 10,000-liter perfusion reactor. The cell culture broth will then be clarified through centrifugation and continuously fed into downstream purification unit operations of protein A chromatography, anion exchange chromatography, cation exchange chromatography, and diafiltration (see *Figure 1*). A water-for-injection

purification system will also be designed for the facility in order to provide sterile water for each production step.

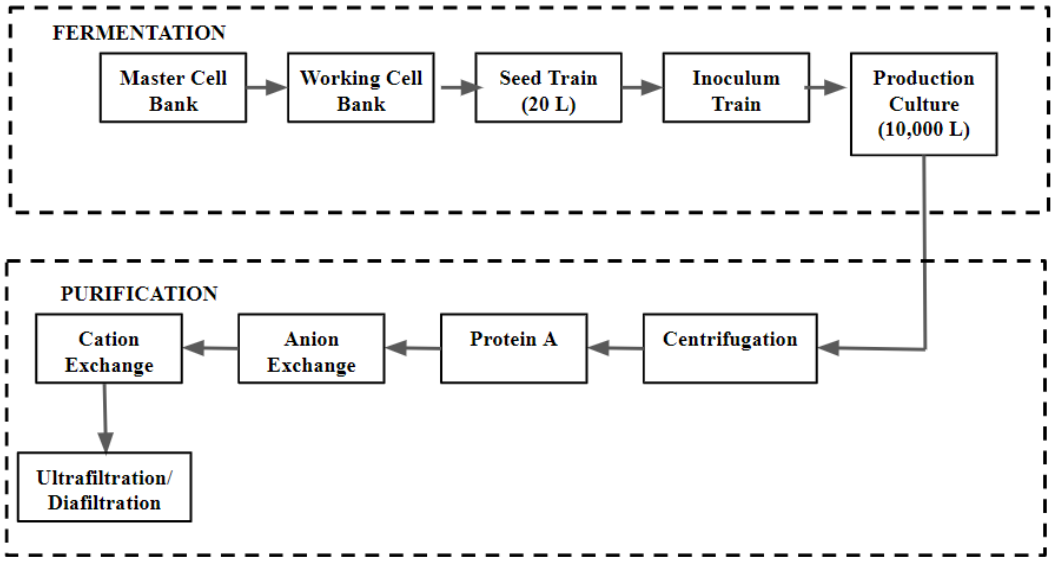

Figure 1: Generalized process flow diagram for the production of monoclonal antibody. Adapted from Petrides, Siletti, Carmichael, & Koulouris, 2014.

Aspen Plus V11 and MATLAB will be used to model the several unit operations involved in Keytruda production while implementing theories of bioseparations, kinetics, transport phenomena, and thermodynamics. Our team will need to estimate projected Keytruda demands in order to calculate how much drug should be produced to appropriately size equipment. We will produce a Design Basis Memorandum in Fall 2019 and complete the technical design in Spring 2020.

STS Topic:

The STS proposal will focus on the role that patents play in the innovation, pricing, and accessibility of the protein therapeutic, insulin, in the United States. More than 30 million Americans have diabetes, which creates a market value of more then $327 million (Cefalu et al., 2018). Additionally, diabetes was the seventh leading cause of death in the U.S. in 2015 (Centers

for Disease Control and Prevention, 2017). The sheer amount of people that this drug impacts in the U.S. emphasizes how its lack of access is endangering to the lives of many. This research topic is important because a better understanding of how patents benefit and/or hinder drug access and innovation will help provide solutions to this growing problem.

The main stakeholders in this analysis are pharmaceutical companies that manufacture insulin, the United States government, and the consumers of insulin. The drug companies that produce insulin and/or have patents relating to the manufacturing of insulin are Eli Lily, Novo Nordisk, and Sano (Belluz, 2019). Drug companies are responsible for the pricing, distributing and impact the market through use of specific patents. The United States government is another major stakeholder as it enacts guidelines for how patents are filed and how companies can use their patents economically. The final stakeholder is the millions of Americans with diabetes that need insulin. This stakeholder will emphasize how patents have increased the quality/innovation of insulin, and/or limited peoples the access to insulin. All three stakeholders will give a clear picture into the current market for insulin and how patents have influenced access and innovation for the drug.

The STS theories that will be used to analyze the topic will include Political Technology, as well as the Technological Fix. The Political Technology framework will look at the laws surrounding patents and insulin in the United States. This framework is based around the fact that technologies are interwoven into modern politics (Winner, 1980). Insulin falls into the framework as the first type of political artifact described by Winner, in which the technical device becomes a way of settling issues in a certain community (Winner, 1980). In the context of insulin this means that the drug is used to settle the problem of a specific community, referring to the diabetic patients in the United States. An analysis of how companies' patents, and the U.S.

laws, influence how insulin is used and accessed will be explored using this framework. The political technology framework will also look at how U.S. politics and government institutions surrounding drug patents allow for companies to profit off of insulin, and influence the economic market. Some critiques from literature of this framework indicate that Winner's definition of politics was too broad resulting in his discussion taking to account some social, and cultural implications as well (Donnelly, 1990). With the critique in mind, for the duration of the paper "politics" will refer to factors that both the U.S. government and large corporations take, that impact the economics of the drug industry, innovation, and how people access insulin.

The second framework that will be implemented is the Technological Fix. This framework implies that technology is often implemented to solve problems, even those nontechnical in nature (Markusson et. al, 2017). The Technological Fix is also a framework used to describe the use of technology to respond to certain types of social problems (Newberry & Mitcham, 2005). In relation to insulin and this analysis, the framework will be used to analyze how insulin was developed to fix diabetes and prevent deaths from the disease (Scott, 2016). The framework will then explore the social, and economic factors that have hindered the drug from eliminating deaths from diabetes in the United States. One literary critique of this framework is that Technological Fix is often assumed to refer to "cheap" technological fixes to problems that do not affect society economically or socially (Markusson et. al, 2017). This assumption results in an incomplete analysis of the technology in question (insulin). Therefore, the social and economic implications of insulin as it relates to the problem of accessibility will be addressed. Additionally, the report will go in-depth into why insulin is not being able to reach a wide variety of consumers, as well as explore how patents have hurt or helped in the development and

distribution of insulin. This framework will also look into other social and political "fixes" for the insulin accessibility issue as it pertains to patents.

Research Question and Methods:

The main STS research question that will be explored is, how do patents influence people's access to insulin as well as, promote the innovation of insulin in the United States? The methods that will be used to analyze this question will include a historical case study on how insulin accessibility has changed throughout time to give a better understanding of the current landscape surrounding the drug. Additionally, a political analysis of the current laws surrounding patents on pharmaceuticals will be discussed. The political analysis will give readers a better understanding of how patents on insulin have been used to legally limit access or improve innovation. The final method that will be used in the paper will be wicked problem framing in order to understand the root problem in the lack of access to insulin, and how patents can help or hinder access to the drug. These three methods will be used because they will give a clear description of how patents function politically and in conjunction with drug pricing. The historical case study will help answer the research question by exploring how in the past, patents have influenced drug innovation, and pricing. The historical case study will give a better understanding of how patents have, and will impact insulin's price. The political analysis will allow a better understanding of the current political climate surrounding patents and insulin. Finally, the Wicked Problem framing method will give general overview of how patents can help or hinder the current problem of insulin accessibility. The majority of research for the project should be completed by the end of February 2020. This includes collecting information on past and previous laws surrounding patents on insulin, as well as a full description on how insulin

prices have changed. A full analysis of all research materials and sources should be gathered, and placed in the report by the end of Spring 2020.

Conclusion:

In conclusion, the technical deliverable for this project will be the design of a plant containing a perfusion reactor, single use equipment, as well as a water purification system for the production of Keytruda in Ireland. The STS deliverable will be an in depth analysis of the roles that patents play in the access, and innovation of insulin. By the end of the report, recommendations for changes to the patent system to improve accessibility and maintain innovative practices will be given. Once these deliverables are met, the technical problem of designing an optimized plant for the protein therapeutic, Keytruda, will be solved, and a feasible way to produce an increased amount of the drug for numerous patients will be realized. The STS problem will be solved through a better understanding of the insulin market and patents in the United States.

References:

Awwad, S., & Angkawinitwong, U. (2018). Overview of Antibody Drug Delivery. *Pharmaceutics*, *10*(3).

Belluz, J. (2019, May 24). The absurdly high cost of insulin, explained. Retrieved October 22, 2019, from https://www.vox.com/2019/4/3/18293950/why-is-insulin-so-expensive.

Bielser, J.-M., Wolf, M., Souquet, J., Broly, H., & Morbidelli, M. (2018). Perfusion mammalian cell culture for recombinant protein manufacturing – A critical review. *Biotechnology Advances*, *36*(4), 1328–1340.

Bryon , N., & Carl, M. (2005). In *Encyclopedia of Science, Technology, and Ethics* (p. 1800). Retrieved from https://collab.its.virginia.edu/access/content/group/484deb3f-d8f1-405a-8b1c-5541ca7dd540/Readings/Newberry%20-%20TechnologicalFix.pdf

Cefalu, W. T., Dawes, D. E., Gavlak, G., Goldman, D., Herman, W. H., Nuys, K. V., … Yatvin, A. L. (2018, June 1). Insulin Access and Affordability Working Group: Conclusions and Recommendations. Retrieved October 22, 2019, from https://care.diabetesjournals.org/content/41/6/1299.

Centers for Disease Control and Prevention. (2017, July 18). [Article]. Retrieved from https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html

Donnelly, R. W. (1990). *The politics of technology: A critique of the work of Langdon Winner*. 135.

MarketWatch. (2019). Protein Therapeutics Market Size - Industry Share Outlook 2023. (2019, July 15). Retrieved October 30, 2019, from https://www.marketwatch.com/press-release/protein-therapeutics-market-size---industry-share-outlook-2023-2019-07-15?mod=mw_quote_news.

Markusson, N., Dahl Gjefsen, M., Stephens, J. C., & Tyfield, D. (2017). The political economy of technical fixes: The (mis)alignment of clean fossil and political regimes. *Energy Research & Social Science*, *23*, 1–10. https://doi.org/10.1016/j.erss.2016.11.004

Melanoma Research. (2016, May). [Article]. Retrieved from https://www.curemelanoma.org/patient-eng/melanoma-treatment/immunotherapy/pembrolizumab-keytruda-/

Merck & Co. (2019). How KEYTRUDA® (pembrolizumab) Works. Retrieved October 29, 2019, from Keytruda website: https://www.keytruda.com/how-does-keytruda-work/

Nathan-Kazis, J. (2019, October 4). Mercks Keytruda Will Become Best-Selling Drug Worldwide, Research Group Says. Retrieved October 22, 2019, from https://www.barrons.com/articles/mercks-keytruda-will-become-best-selling-drug-worldwide-research-group-says-51570204530.

National Cancer Institute, (2015). Cancer Statistics. Retrieved October 28, 2019, from National Cancer Institute website: https://www.cancer.gov/about-cancer/understanding/statistics

Petrides, D., Siletti, C., Carmichael, D., & Koulouris, A. (2014). *Biopharmaceutical Process Optimization with Simulation and Scheduling Tools*. 154–187.

Rappold, R. S. (2019, July 18). Families Cross Borders in Search for Affordable Insulin. Retrieved October 22, 2019, from https://www.webmd.com/diabetes/news/20190718/spiking-insulin-costs-put-patients-in-brutal-bind.

Rosenfeld, J. (2019, April 3). The rising price of insulin. Retrieved October 22, 2019, from https://www.medicaleconomics.com/article/rising-price-insulin.

Scott, D. (2011). The Technological Fix Criticisms and the Agricultural Biotechnology Debate. *Journal of Agricultural and Environmental Ethics*, *24*(3), 207–226. https://doi.org/10.1007/s10806-010-9253-7

18) The Irish Times. (2018). Cancer drug Keytruda drives profit at Merck. Retrieved from https://www.irishtimes.com/business/health-pharma/cancer-drug-keytruda-drives-profit-at-merck-1.3480278.

19) Winner, L. (1980). Do Artifacts Have Politics? *Daedalus*, *109*(1,), 121–136.